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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/975,881	10/12/2001	Valentin K. Gribkoff	CT-2590-NP	9722

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EXAMINER

STOCKTON, LAURA LYNNE

ART UNIT	PAPER NUMBER
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1626

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/975,881	GRIBKOFF ET AL.
	Examiner	Art Unit
	Laura L. Stockton, Ph.D.	1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-65 is/are pending in the application.
- 4a) Of the above claim(s) 46-65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-65 are pending in the application.

Election/Restrictions

Applicants' election without traverse of Group I, and the species of Example 2 (the structure of BMS-204352 on pages 13 and 27), in the response filed October 1, 2003 is acknowledged.

Subject matter not embraced by elected Group I and claims 46-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Election was made **without** traverse in the response filed October 1, 2003.

It is suggested that in order to advance prosecution, the non-elected subject matter be cancelled when responding to this Office Action.

Any rejection of the claims under the judicially created doctrine of obviousness-type double patenting over U.S. Pat. 5,565,483 and U.S. Pat. 5,602,169 is overcome by the filing of the two (2) Terminal Disclaimers on April 24, 2003. The terminal disclaimers have been accepted and recorded.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 12-17, 19-26, 28-40 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Hewawasam et al. {U.S. Pat. 5,565,483} and Hewawasam et al. {U.S. Pat. 5,602,169}.

Hewawasam et al. '483 disclose Example 14 (column 25) that is an opener of the large-conductance calcium-activated potassium channels (also known as maxi-K channels) and is useful in the treating of disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels (column 1, lines 5-13, 31-33 and 47-53; column 13, lines 41-53; and column 25, lines 40-52).

Hewawasam et al. '169 disclose Example 14 (column 26), Example 37 (column 31) and Example 38 (column 31) which are openers of the large-conductance calcium-activated potassium channels and are useful in the treating of disorders (e.g., ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels (column 1, lines 12-19, 37-39 and 53-59; column 3, lines 23-63; column 13, lines 41-53; and column 26, lines 36-51; column 31, lines 26-56).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hewawasam et al. {U.S. Pat. 5,565,483} and Hewawasam et al. {U.S. Pat. 5,602,169}.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicants claim a method of treating a disease or disorder characterized by high intracellular calcium levels comprising providing an effective amount of an opener of maxi-K potassium channels (e.g. fluoro-oxindole and chloro-oxindole compounds). Each of Hewawasam et al. '483 (column 1, lines 5-13, 31-33 and 47-53; column 13, lines 19-53; and column 25, lines 40-52) and Hewawasam et al. '169 (column 1, lines 12-19; column 3, lines 23-63; column 13, lines 19-53; Example 14 in

column 26, lines 36-51; and Examples 37 and 38 in column 31, lines 26-56) teach fluoro-oxindole compounds, which are openers of the large-conductance calcium-activated potassium channels (also known as maxi-K channels) and are useful in the treating of disorders (e.g. ischemic stroke, traumatic brain injury, etc.) which are responsive to the opening of the potassium channels.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between some of the products taught by the Hewawasam et al. references and the products instantly claimed is that of generic description (e.g., see instant claim 8).

The difference between some of the products taught by the Hewawasam et al. references and the products instantly claimed (e.g., see instant claim 11) is that of fluoro-oxindole instead of chloro-oxindole.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

The indiscriminate selection of “some” among “many” is *prima facie* obvious. The motivation to make the claimed compounds derives from

the expectation that structurally similar compounds would possess similar activity (e.g., an opener of maxi-K channels).

In *Ex parte Wiseman*, 98 USPQ 277 (1953), it was held that compounds are rejected over prior art when the difference between the claimed compounds and the compounds of the prior art is two fluorine atoms versus chlorine atoms. The basis of this reasoning is that fluorine and chlorine are both halogen elements from the seventh group of the periodic system and the claimed compound is thus an analogue or an isologue of that disclosed in the prior art. The compounds are expected to possess similar properties differing only in degree.

One skilled in the art would thus be motivated to prepare products embraced by the Hewawasam et al. references, or alternatively, prepare the chloro-oxindole products instead of the fluoro-oxindole products, to arrive at the instant claimed invention with the expectation of obtaining products which would be useful in treating disorders such as stroke, traumatic brain injury, etc. The instant claimed invention would have

been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Response to Arguments

Applicants' arguments filed April 24, 2003 have been fully considered. In regard to the rejections of the claims under 35 USC §§ 102 and 103, Applicants argue that the two Hewawasam patents fail to teach calcium-dependent maxi-K channel openers which exhibit specific opening of these channels at high levels of intracellular calcium, but which have little effect on these channels in cells having low intracellular levels.

All of Applicants' arguments have been considered but have not been found persuasive. Applicants claim a method of treating a disease or disorder characterized by high intracellular calcium levels comprising providing an effective amount of an opener of maxi-K potassium channels (e.g. fluoro-oxindole and chloro-oxindole compounds).

Applicants disclose diseases/disorders that could be treated by an oxindole opener of maxi-K channels are stroke, global cerebral ischemia, traumatic brain injury, etc. (see instant claim 4).

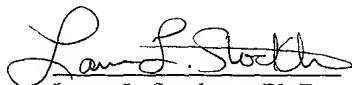
Each of the two Hewawasam patents disclose and claim pharmaceutical methods of administering oxindole compounds which are modulators of the large-conductance calcium-activated (Maxi-K) channels. The diseases/disorders which can be treated by administering oxindole modulators of the large-conductance calcium-activated (Maxi-K) channels are ischemic stroke, traumatic brain injury, etc. Such oxindole compounds disclosed are Example 14 (column 25 in Hewawasam et al. '483) and Example 37 (column 31 in Hewawasam et al. '169). Note, Example 37 in Hewawasam et al. '169 is the same compound of the elected species of Example 2 in the instant application. A compound and its properties are inseparable. *In re Papesch*, 137 USPQ 43 (CCPA 1963). Therefore, the same compounds are used to treat the same disorders/diseases. Hence, the instant claimed invention is anticipated by the prior art and found obvious to one skilled in the art.

The elected species of Example 2 (the structure of BMS-204352 on pages 13 and 27) is not allowable. See, for instance, Example 37 in column 31 of U.S. Pat. 5,602,169.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (703) 308-1875. The examiner can normally be reached on Monday-Friday from 6:00 am to 2:30 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

A handwritten signature in cursive script, reading "Laura L. Stockton", written over a horizontal line.

Laura L. Stockton, Ph.D.
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

December 22, 2003